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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/402,394	03/10/95	DORSCHUG	M 02481.0790-0

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EXAMINER	
SAOUD, C	
ART UNIT	PAPER NUMBER
1801	38

DATE MAILED: 01/07/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 10/2/96.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days, whichever is longer,~~ from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 21-23, 25-27, 31 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 21-23, 25-27, 31 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

★ U.S. GPO: 1996-410-238/40050

Transitional After Final Practice

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on October 2, 1996 has been entered.

DETAILED ACTION

2. Applicant's amendment filed October 2, 1996 has been entered. Claim 31 has been added and claims 21, 22, 25 and 26 have been amended. Claims 21-23, 25-27 and 31 are pending in the instant application and are under consideration.

3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Response to Arguments

4. Applicant's arguments filed October 2, 1996 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

5. Claims 21-23, 25-27 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim limitation of "under conditions where no crystals are formed" is new matter because there is nothing in the instant specification to serve as a basis to exclude conditions where no crystals are formed even though this is a property the example at pages 15-16. This rejection was made in paper #35 and is again being made with the inclusion of this limitation at this time. Applicant cites case law which states "it is not new matter to amend the specification and drawings to make explicit a disclosure which was implicit in the application as filed." However, the instant application is intending to impose a negative limitation on the claims which is not implicit from specification as filed. M.P.E.P. 2173.05(I) is directed to claims containing negative limitations and states:

> Any negative limitation or exclusionary proviso must have basis in the original disclosure. See Ex parte Grasselli , 231 USPQ 393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement.

Therefore, the limitation of "under conditions where no crystals are formed" is new matter, absent clear and convincing evidence to the contrary.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 21-23, 25-27 and 31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Mai et al., Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332) essentially as applied to the claims in the prior Office actions (paper #'s 32 and 29).

Applicant states that their invention differs from the art cited because the pending claims are directed to (1) a process for preparing mono-Arg-insulin and human insulin, (2) reaction conditions such that the process takes place in an aqueous buffer wherein crystals of the intermediary products are not obtained, and (3) a process which permits simultaneous addition of trypsin and carboxypeptidase to the reaction mixture. These arguments (found at page 8 of Applicant's response) are not persuasive and each point will be addressed below.

Markussen was cited as a reference because it discloses methods of producing insulin as well as disclosing insulin precursors. Markussen provides a generic formula which encompasses Applicant's mono-Arg-insulin, but does not specifically teach mono-Arg-insulin. Applicant states that "there is no teaching in the art that could motivate the skilled artisan to select the mini-proinsulin of formula I as the starting material to produce insulin." This is not the case because Grau ('332) specifically discusses the mono-Arg-insulin species of mini-proinsulin and that it is exceptionally stable to further tryptic degradation (col. 2, lines 10-12). Grau ('332) not only suggests the compound of the instant application, but provides motivation to obtain it because it is "exceptionally stable". Markussen alone does not make mono-Arg-insulin obvious, but the teaching of Grau ('332) provides motivation to one of ordinary skill in the art to make mono-Arg-insulin as well as use it as an intermediary for the production of insulin because it is "exceptionally stable", absent clear and convincing evidence to the contrary. Applicant states that mere knowledge of the existence of mono-Arg-insulin does not provide the requisite motivation to modify the process of Markussen; however, the statement that mono-Arg-insulin is "exceptionally stable" and because this species of mini-proinsulin is encompassed by the disclosure of Markussen makes it an ideal and obvious choice for use in the methods disclosed for the production of insulin.

Applicant argues that improper hindsight was used in making the rejection which appears in the instant application. As pointed out, when prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself (page 10 of Applicant's response). The motivation for the combination of Markussen and Grau ('332) has been clearly spelled out in the previous rejection; Markussen teaches a generic formula for mini-proinsulin and Grau ('332) teaches a species of this mini-proinsulin which is mono-Arg-insulin. This species is "exceptionally stable" and therefore, one of ordinary skill in the art would be motivated to use this mono-Arg-insulin in order to prepare insulin as well as being motivated to make mono-Arg-insulin because of this exceptional stability. Applicant states that "there is no reason why one would modify the Markussen process to yield mono-Arg-insulin". One of ordinary skill in the art would be motivated to produce mono-Arg-insulin because Grau ('332) teaches that mono-Arg-insulin is "exceptionally stable", and therefore, it would be desirable to make this form of insulin so as to have a form of insulin which is not subject to degradation. Markussen teaches methods for making insulin and Grau teaches an "exceptionally stable" form of insulin so it would have been *prima facie* obvious to make mono-Arg-insulin or to use mono-Arg-insulin with the methods of Markussen. The motivation and reasoning for using mono-Arg-insulin as well as the motivation and reasoning for obtaining mono-Arg-insulin are

both logical as well as suggested by concrete evidence of record in the prior art, therefore, the rejection is not a case of hindsight reconstruction (see page 11 of Applicant's arguments).

With regard to point #3 (simultaneous addition of trypsin and carboxypeptidase to the reaction mixture), Applicant states that there is no teaching or suggestion in the prior art which would lead to the simultaneous use of these enzymes." This argument is not persuasive because Grau ('684) teaches the process wherein trypsin and carboxypeptidase B were added together and resulted in the production of mature insulin from proinsulin (see column 5, lines 57-59).

Finally, with regard to point #2 (reaction conditions such that the process takes place in an aqueous buffer wherein crystals of the intermediary products are not obtained), Applicant submits that the cited art fails to support the contention of the previous Office action. However, the basis for this limitation in the claims comes from pages 15-16 of the instant specification which state:

> the mono-Arg insulin is precipitated from the product-containing fractions after 1:1 dilution with H_2O by adding 10 ml of 10% $ZnCl_2$ per 1 l and adjusting the pH to 6.8. The precipitate separated by centrifugation is crystallized at pH 6 from a buffer composed of 1 g/l of phenol, 10.5 g/l of citric acid and 200 mg/l of $ZnCl_2$.

The examples in Markussen demonstrate that the processes take place in an aqueous buffer (acetic acid) with the isolation of the protein via precipitation with acetone (see column 18, lines 42-68). As stated in the Office action of paper #29, "the limitations

where no crystals are formed would be met as the prior art does not absolutely require crystallization and furthermore, the methods do not preclude additional steps where crystallization occurs." Markussen does not require crystallization nor does the methods of Markussen preclude additional steps where crystallization occurs. The method of Grau ('684) results in the crystallization of mono-Arg-insulin, as pointed out in Applicant's response, but using the mono-Arg-insulin of Grau ('332) in the method of Markussen would not result in crystals being formed. The final product could be crystallized by methods well-known in the art in order to obtain a crystallized mono-Arg-insulin or crystallized insulin, because it is well-known in the art to crystallize proteins for storage purposes, etc. Therefore, the invention as a whole would have been *prima facie* obvious at the time it was made, absent clear and convincing evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 4PM.

The fax phone number for this Group is (703) 308-0294. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Christine Saoud, Ph.D.
January 2, 1997
CS

VASU S. JAGANNATHAN
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